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Chapter 13.
DRUGS FOR CARDIAC ARRHYTHMIAS, ANTITHROMBOTIC DRUGS AND LIPID MODULATING DRUGS

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Contents

Drugs for cardiac arrhythmias, antithrombotic drugs and lipid modify drugs are considered in this section.

13.1 Drugs for cardiac arrhythmias

13.1.1 Introduction to cardiac arrhythmia

Sinus rhythm is normal heart rate. **Cardiac arrhythmias** are abnormal rhythms of the heart. **Tachycardia** is faster than normal atrial or ventricular rates, giving atrial tachycardia or ventricular tachycardia. **Flutter** is fast, irregular beats of the atria or ventricles, giving atrial flutter or ventricular flutter. Often the arrhythmias are progressive, tachycardia turns into flutter, and flutter turns into fibrillation. **Fibrillation** is fast, irregular quivers of muscle, without a beat. In **atrial fibrillation**, survival is possible provided the ventricles are still beating normally. Atrial fibrillation can precipitate ventricular fibrillation. **Ventricular fibrillation** can be deadly, as it is not possible to survive without a heart best. **Torsades de pointes** are drug-induced ventricular tachycardia. Infarcted or ischemic areas of myocardium can precipitate arrhythmias.

Cardiac arrhythmias are common. **Atrial fibrillation** affects 0.4% of the general population, but the incidence increases with age to 2-5% of persons over 60 years of age and 10% of those older than 70 years. Ten percent of the survivors of myocardial infarction (MI, heart attack) die during the subsequent year, mostly of cardiac arrhythmias. Fifty percent of patients with heart failure undergo a **sudden death**, which may be due to cardiac arrhythmia.

13.1.2 Cardiac action potentials

To understand how the drugs used to treat cardiac arrhythmias work, it is necessary to know about **cardiac action potentials** and the mechanisms of arrhythmias. Cardiac action potentials are different in the sino-atrial node (pacemaker) and the His-Purkinje conducting system to the ventricles. At the **sino-atrial node**, there is a **slow response** made up of a gradual depolarization, and then more definite depolarisation, followed by repolarisation (Figure 13.1), and this process is continual. The more definite depolarization is due to the opening of Ca^{2+} channels with Ca^{2+} entry into the cells. With every slow response, a heart beat is initiated.

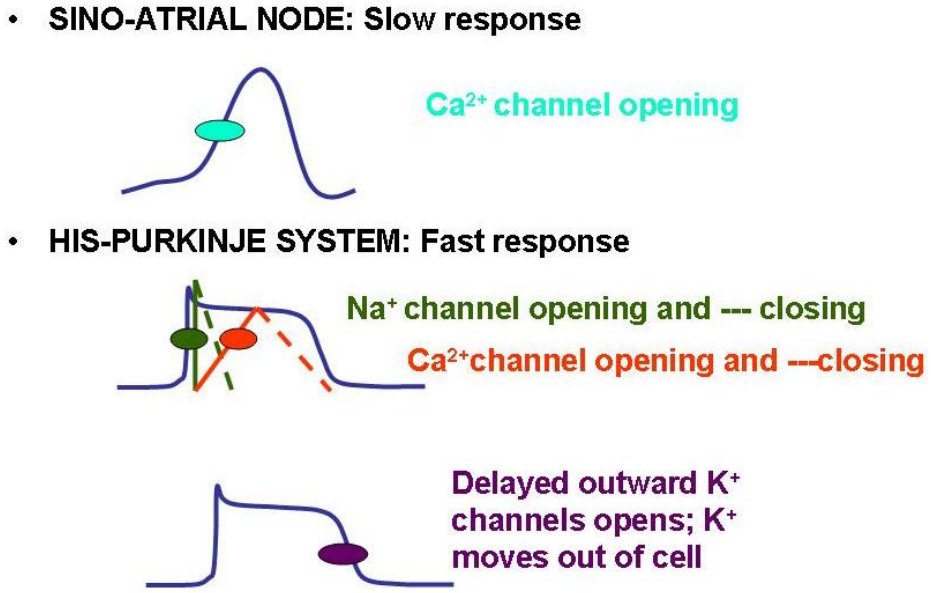

Figure 13.1 Cardiac action potentials

The His-Purkinje system is responsible for conducting the impulse around the heart causing it to beat**.** In the **His-Purkinje system,** there is a more complex action potential; initially there

is a resting membrane potential, then a rapid depolarisation that gives a **fast response**, followed by **3 phases of repolarisation** (rapid, slow, and delayed) (Figure 13.1.1). The **rapid depolarisation** is due to **sodium channels** opening with Na^+ moving into the cardiac cells. **Calcium channels** open letting Ca^{2+} into the cell and then close during the **slow phase of repolarisation**. During the **delayed repolarisation** delayed **outward K^+ channels** open, and K^+ moves out of the cardiac cells. Thus, drugs that act at Na^+, Ca^{2+}, and K^+ channels can modify cardiac action potentials and, consequently, alter the activity of the heart. In particular, the ion channel modulators can alter cardiac arrhythmias.

13.1.3 Mechanisms of arrhythmia

There are several **mechanisms of arrhythmias**. The most important cause of cardiac arrhythmias is **cardiac injury**, which includes the acute injury associated with a heart attack, and the chronic injury due to the ischemic heart disease associated with angina. Other factors can also contribute to arrhythmias including **hypoxia, acidosis**, and **increases in extracellular K^+ and/or Ca^{2+}.** Stress induced increase in the activity of sympathetic nervous system, with an increased release of noradrenaline and adrenaline and activation of cardiac β-adrenoceptors, can also precipitate cardiac arrhythmias.

Cardiac arrhythmias are either disorders of impulse formation or disorders of impulse conduction. **Disorders of impulse** are of 3 types. Firstly, there is a **heart block**, where injury to sino-atrio node or atrio-ventricular node causing heart to stop. Usually, to start with this is only for short period, during which the person collapses, and then regains consciousness when the heart starts to beat again, but heart blocks do tend to be progressive; occurring more often and for longer. The treatment for advanced heart blocks is a pacemaker. The second disorder of impulse is an **increased firing rate originating in the pacemaker region**. Drugs that **inhibit the SLOW response** i.e. the calcium channel, at the sino-atrio node are useful in this condition. Thirdly, there is the **development of ectopic pacemaker**, a pacemaker outside of sino-atrial node. Ectopic pacemaker usually develops in the specialised His Purkinje conduction system of the atria or ventricles. Drugs that **inhibit the FAST response** of the specialised conducting system are useful in treating ectopic pacemakers.

Disorders of conduction are due to damage in the **Purkinje conducting system**. In the **normal heart**, impulses arise in the sino-atrial node (pacemaker) and spread around with atria to the atrio-ventricular node, and then around the ventricles to they meet and die out. Impulses leave in their wake refractory tissue, and refractory tissue cannot be re-excited for 200-500 msec. When the last part of heart is excited X, the impulses are surrounded by refractory tissue, and the impulses die out, and there is a period of electrical quiescence. Each of these impulse cycles is associated with a heart beat, and the process is repeated 60 to 80 per min to give a heart rate of 60 to 80 beats per min.

The most common disorder of impulse conduction is **functionally defined re-entry**. In this there is damage leading to a unidirectional functional block, the impulse can go through one way, but not the other. Thus, the impulse dies out at the damage area. The impulses coming from the other area does not meet one at the bottom of the heart, and just keeps going (Figure 13.2). The impulse can **re-enter the ventricular circuit**, and cause further activation with quivers of the heart muscle.

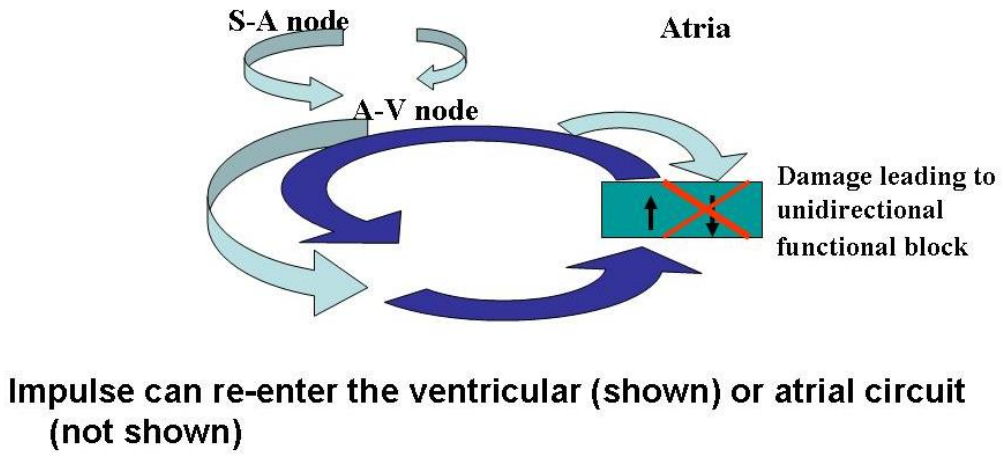

Figure 13.2 Functional defined re-entry (Copyright QUT, Sheila Doggrell)

Treatment for unidirectional blocks is most commonly, to **turn a unidirectional block into a bidirectional block**. With this approach, the impulses will die out at the damaged area rather than the apex of the heart. The benefit is due to preventing the impulse from re-entering. The other approach is to increase excitability or conduction to overcome block, and this returns to near normal function, with the impulses dying out at the apex. The problem with this approach is that if you increase excitability too much, and ectopic centre will develop in the conduction system giving an extra beat. Thus, although not the best method, turning a unidirectional block into a complete block is the safest approach with drug intervention.

Anti-arrhythmic drugs are divided into 4 classes.

13.1.3 Class I

Class I agents block Na^+ channels, the channels involved in the rapid depolarisation in the Purkinje system. Examples of class I Na^+ channel blocker is **lignocaine**. Lignocaine is also known as lidocaine, and is also used as a local anaesthetic, where the effect is also due to blocking Na^+ channels. The Na^+ channel blockers have no effect on sinus rhythm, as Ca^{2+} channels predominantly control sinus rhythm. Lignocaine is used in **serious ventricular arrhythmias**, where they decrease the excitability of the conduction system.

13.1.4 Class II

Class II agents are β-adrenoceptor antagonists. As mentioned before, a whole range of things can cause activation of the sympathetic nervous system; myocardial infarction, stress, exercise, pheochromocytoma (adrenaline secreting tumours), and hyperthyroidism. With sympathetic nervous system activation, there is the release of noradrenaline and adrenaline and the activation of cardiac β-adrenoceptors, which can initiate or make worse tachyarrhythmias. β_1-adrenoceptor antagonism leads to decreased effects of the sympathetic nervous system (SNS) on the heart, and a reduction in tachyarrhythmias.

Of the β-adrenoceptor blockers, **propranolol** is the one that is often preferred in cardiac tachyarrhthymias. Propranolol is a non-selective β-adrenoceptor blocker that may have some **Na^+ channel blocking activity**, and this Na^+ channel blocking activity may contribute to the benefit by decreasing excitability and conduction. Propranolol is used in the treatment of **tachyarrhythmias**, where an overactive sympathetic nervous system is implicated.

Esmolol is an ultra-short acting β-adrenoceptor blocker used intravenously to treat **atrial flutter** and **atrial fibrillation** associated with operations. When atrial flutter or fibrillation occurs during an operation, esmolol can be administered intravenously, to bring the heart back to normal sinus rhythm, and then the infusion can be stopped and the esmolol is rapidly metabolised.

13.1.5 Class III

Class III anti-arrhythmic agents block the delayed outward rectifying K^+ channel. **D-sotalol**, the D-isomer of the β-adrenoceptor blocker racemic sotalol, blocks the **delayed outward rectifying potassium channel** to prolong the action potential in the Purkinje system (Figure 13.3). In a **normal heart**, D-sotalol prolongs the repolarisation, but this has little effect as there is a period of quiescence between action potentials (and between heart beats). Arrhythmias are often due to re-excitation in what should be the quiescence phase. By prolonging the repolarisation, D-sotalol decreases the likelihood of re-excitation (Figure 13.3).

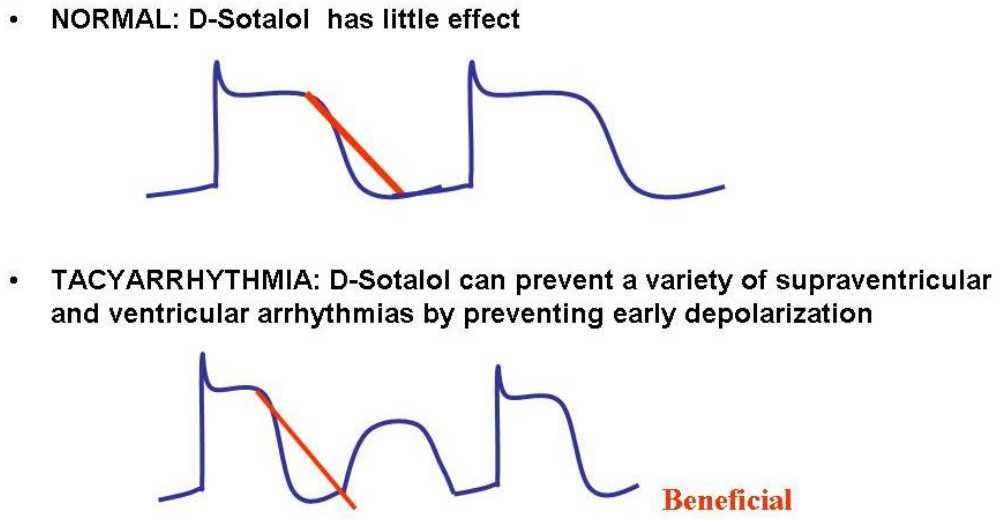

Figure 13.3 Mechanism of D-sotalol (Copyright QUT, Sheila Doggrell)

D-sotalol is useful in a variety of **supraventricular** (arising in the atria) and **ventricular arrhythmias**.

13.1.6 Class IV

Class IV anti-arrhythmic agents are Ca^{2+} channel blockers. **Verapamil** preferentially blocks **cardiac Ca^{2+} channels** over vascular Ca^{2+} channels. Thus, verapamil inhibits the inward Ca^{2+} current associated with pacemaking. Verapamil also slows conduction through the atrio-ventricular node. Verapamil is used in arrhythmias associated with **increased excitation of sino-atrio** or **atrio-ventricular node**. Verapamil is active after oral administration but does undergo extensive first pass liver metabolism. Verapamil can also be used intravenously in an emergency.

13.1.7 Amiodarone

Amiodarone is a unique anti-arrhythmic that has activity in all classes. Thus, amiodarone is a potent **K^+ channel blocker**, including blocking the delayed outward rectifying potassium channel. However, amiodarone is also a **Na^+ channel blocker**, and a **Ca^{2+} channel blocker**,

mimicking the effect of verapamil. Amiodarone is also a **blocker of α- and β-adrenoceptors**. Finally, an unwanted mechanism of amiodarone is that it is an analog of thyroid hormone. Thus, amiodarone interacts with nuclear thyroid hormone receptors in an inhibitory way, such that many of the adverse effects of amiodarone mimic those of hypothyroidism.

Amiodarone is used orally in **recurrent ventricular tachycardia/fibrillation**, particularly when the arrhythmia is resistant to other drugs. Also, amiodarone is used orally to **convert atrial fibrillation into normal sinus rhythm**. Amiodarone is used intravenously for the **termination of ventricular or supraventricular arrhythmias in an emergency**.

In clinical trials, it has been shown that preventative oral use of amiodarone, after myocardial infarction or in heart failure, **reduces sudden death**, which is usually arrhythmic death. However, amiodarone is not standard therapy after myocardial infarction or in heart failure, probably because it has many adverse effects, which means people do not like taking it, and the benefits may not exceed the risks.

Amiodarone is very lipid soluble, and large amounts accumulate in fat tissues, and are only slowly released. The adverse effects associated include **pulmonary toxicity** in 2-17% of patients and **hypothyroidism** in 2-10% of patients, but severe arrhythmias are rare.

13.1.8 Adenosine

Adenosine is a naturally occurring substance that **slows sinus node activity and conduction through the atrioventricular node**. It is produced in ischemia, and slows the heart rate.

Adenosine can also be used clinically to **slow heart rate**. Adenosine has a short duration of action. The short duration limits the used of adenosine to the emergency situation for acute treatment of supraventricular arrhythmias. In an emergency, adenosine is used intravenously, for the acute treatment of supraventricular (atrial) arrhythmias, where its rapid onset of action is a major advantage.

13.2 Anti-thrombotic drugs

This section concerns the anti-thrombotic drugs, and there are 3 groups these, the **anti-platelet agents**, which are used to prevent platelet-platelet aggregation at the start of thrombus formation. The second group are the **anti-coagulants**, to prevent coagulation, which often occurs around excessive platelet-platelet aggregation. The third group are the **fibrinolytics (**also known as **thrombolytics)**, which are used after clots have formed to cause heart attack or stroke, to breakdown the clots and restore normal blood flow.

13.2.1 Thrombus formation

On the **arteriolar side to the circulation**, white/arterial thrombus form, and the whiteness is due to the presence of **platelets**, which are white cells. When there is damage to blood vessel wall, this can lead to bleeding. In order to repair blood vessels, platelets stick to the damaged area, and then **platelet-platelet aggregation** occurs at the site. Normal platelet aggregation is good, as it is involved in the repair process. However, if the platelet aggregation is excessive, this may occlude the areas of slower arterial blood flow. This leads to more local bleeding, and the capture of red blood cells can lead to a **red thrombus** around the white thrombus. The problem caused is local ischaemia, with the tissues normally serviced by the

blood vessel no longer receiving oxygen or nutrients. If the artery is a coronary artery supplying the blood to the heart, and the artery has excessive atherosclerosis associated with platelet-platelet aggregation, this leads to transient ischaemic attacks (**typical angina**). Typical angina progresses to be unstable, and then leads to **myocardial infarction**. In the brain, if the carotid artery is similarly affected, this leads to **stroke**.

On the **venous side**, red or venous thrombus form, with the redness due to the **red blood cells**. The blood flow is slower in the veins, and this accounts for the differences in the thrombus. Whereas arteriolar thrombi are layered, blood clot on the venous side, are a mix of platelet-platelet aggregation, fibrin, and red blood cells. Venous thrombi are easily detached, and move in the blood stream to smaller veins, which they block. The problems caused are that thrombi from the calf/deep vein can move around the circulation to cause **embolization** of the pulmonary arteries, which can be deadly.

13.2.2 Platelet aggregation and anti-platelet drugs

When a blood vessel is damaged, this exposes underlying collagen, and platelets stick to collagen. The local mediator responsible for this is thromboxane-A_2 (TXA_2). Thus, there is activation of COX-1 in the platelets, and the intermediates from this, in the presence of thromboxanes synthase form TXA_2. In turn, TXA_2 stimulates TP receptors on platelets to decrease the activity of adenylate cyclase, leading to decreased cAMP, which promotes platelet aggregation (Figure 13.4).

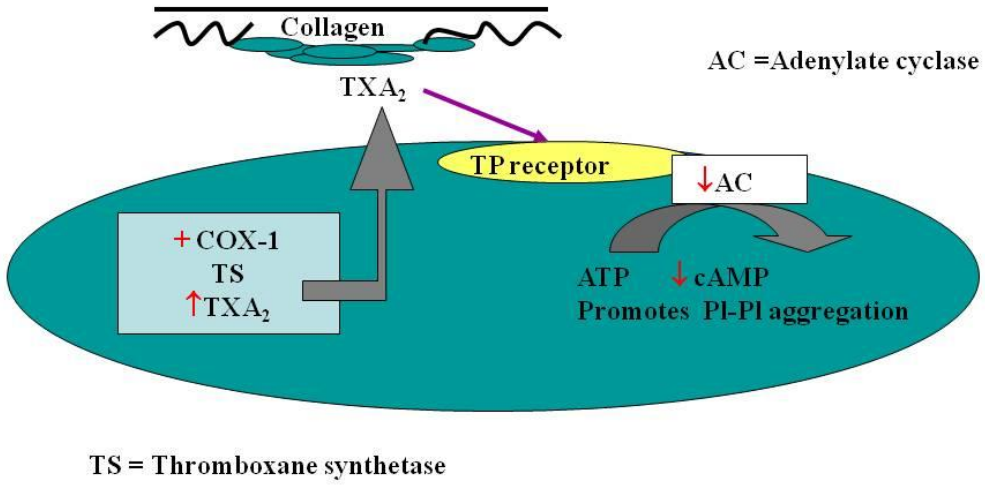

Figure 13.4 Thromboxane and platelet aggregation (Copyright QUT University, Sheila Doggrell)

Platelets do not have a nucleus, and therefore cannot synthesise COX-1. Platelets only have a small supply of COX-1, and once this is used up, there is no more. **Low dose aspirin** irreversible inhibits COX-1 in platelets, decreasing the amount of intermediates available to be converted to TXA_2. This leads to decreased platelet aggregation.

In contrast, **endothelial** cells have a plentiful supply of COX-1, and can synthesise more COX-1. Thus, low dose aspirin has no significant effect on the COX-1 in the endothelial cells or on the production of PGI_2 from the endothelial cells, and PGI_2-mediated inhibition of platelet aggregation. Overall, low dose aspirin only leads to decreased TXA_2 and decreased platelet-platelet aggregation. Low dose aspirin selectively inhibits TXA_2 formation to reduce platelet aggregation. Low dose aspirin is used to **prevent myocardial infarction** and **stroke**. High dose aspirin inhibits both PGI_2 and TXA_2 formation and has NO EFFECT on

platelet aggregation, and will not be useful in the prevention of myocardial infarction or stroke.

Thromboxane is not the only mediator of platelet aggregation. **ADP** is a potent promoter of platelet aggregation, and this effect of ADP is mediated by purinergic P2Y receptors. **Clopidogrel** is an antagonist at P2Y receptors and inhibits ADP-induced platelet aggregation. Clopidogrel reduces cardiovascular events in patients with **unstable angina**, which often leads to coronary artery stenting. Clopidogrel reduces cardiovascular events in patients with unstable angina. As clopidogrel and aspirin inhibit platelet aggregation by different mechanisms, they have an **additive effect**. Clopidogrel is commonly used in **combination with aspirin** to prevent vascular events in subjects with unstable angina, recent myocardial infarction, and in stenting.

Activated platelets develop **glycoprotein IIb/IIIa receptors**, which are receptors for fibrinogen, and mediate aggregation. The GPIIb/IIIa receptor is the final step in platelet aggregation. Inhibiting this receptor will reduce platelet aggregation, regardless of what is causing the aggregation (ADP, TXA_2). **Abciximab** is an antibody to the GPIIb/IIIa receptor, and acts as an antagonist to prevent platelet aggregation. Abciximab is used in combination with aspirin and the anti-coagulant heparin, when **angioplasty or stenting** is undertaken for coronary thrombosis. Used during these procedures, abciximab decreases the incidence of recurrent myocardial infarction and death. Abciximab is administered intravenously, as a bolus, followed by a continuous infusion of a lower dose for 12 hours. The major side effect of abciximab, like all anti-thrombotic drugs is an **increased incidence of bleeding**.

13.2.3 Coagulation

Coagulation is very complicated. The process of coagulation indicated in Figure 23.2 is a much simplified version. Coagulation is a cascade of events which involves several factors from the liver, some of which are vitamin K-independent, and some of which (including **prothrombin**) are **vitamin K-dependent**. There also tissue and platelet factors, which eventually lead to the conversion of prothrombin to thrombin in the circulation. **Factor Xa** is the enzyme necessary for breaking down prothrombin to thrombin. In turn, **Thrombin** is responsible for changing fibrinogen, which is a soluble plasma protein into fibrin, an insoluble protein, which is part of the clot.

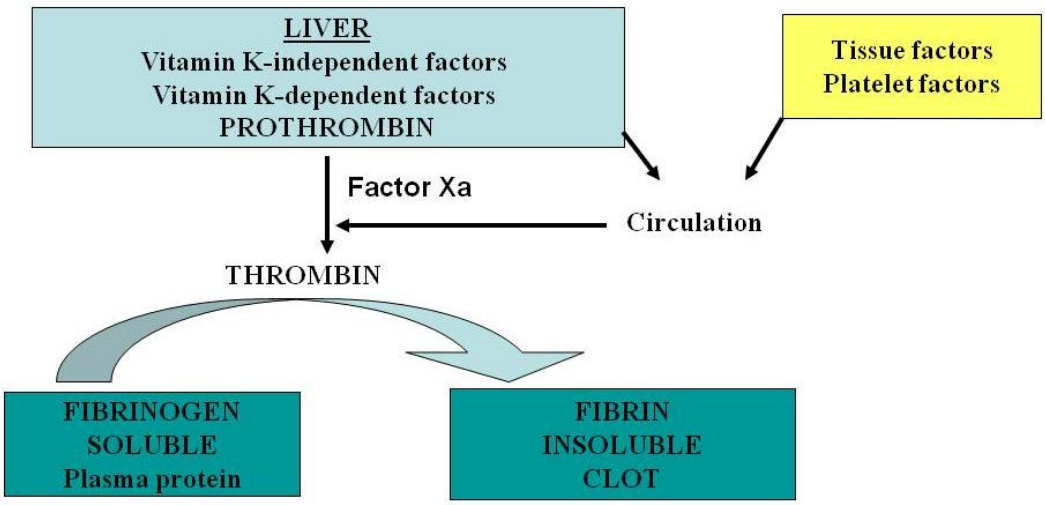

Figure13.5 Coagulation (Copyright QUT, Sheila Doggrell)

13.2.4 Anticoagulants

Heparin is a large (12,000 daltons) endogenous compound found in mast cells. For clinical use, heparin is extracted from porcine intestinal mucosa or bovine lung. Many of the clotting factors are proteases, and heparin inhibits all clotting factor proteases to inhibit clotting quickly. Heparin is precipitated by acid in gut, and not absorbed from gastrointestinal tract, and this means it is ineffective when administered orally. Heparin is used intravenously or subcutaneously.

Low-molecular-weight heparins such as **enoxaparin** (1-10,000 daltons) are made from heparin. Enoxaparin inhibits the final protease in the coagulation cascade, which is **factor Xa** to a greater extent than the other proteases in the cascade. Enoxaparin is used subcutaneously. With heparin, and low-molecular weight heparins, the main toxicity is bleeding, which is just an extension of its therapeutic effect. Heparin and low-molecular-weight heparins are beneficial in unstable angina, and very importantly, they are **effective immediately**, which makes them ideal to use in unstable angina, especially when it is progressing to myocardial infarction, and an immediate anti-coagulant effect is required. Heparins are also used to prevent clotting in surgical and high-risk medical subjects, and in coronary angioplasty.

Warfarin inhibits the formation of vitamin K-dependent factors for coagulation including prothrombin. Warfarin is active after oral administration, and this is a major advantage over heparin, which has to be given intravenously or subcutaneously. However, warfarin is **not effective immediately**, this is a major disadvantage compared to heparin, which is effective immediately.

Warfarin is only effective when existing vitamin K-dependent clotting factors have been broken down, which usually takes more than 36 hours, but is dependent on levels of vitamin K in the body. If vitamin K levels are low, this alone will inhibit coagulation, and further inhibition of coagulation with warfarin may produce haemorrhage. Clinically, **warfarin** use is for prolonged anti-coagulation effect (e.g in the prevention of thrombosis, unstable angina). Heparin and warfarin are often used in sequence, heparin to give an immediate anti-coagulant effect, until the anticoagulant effect of warfarin kicks in. The main toxic effect of warfarin is haemorrhage. The **antidote** to warfarin-induced haemorrhage is **vitamin K** to build up the vitamin K-dependent factors, and promote coagulation.

Direct thrombin inhibitors, such as **dabigatran**, have been developed recently, and may take over some of the present roles of the heparins and warfarin. By directly inhibiting thrombin, dabigatran inhibits the conversion of fibrogen (soluble) to fibrin (insoluble) clot. Dabigatran is active after oral administration, and has an immediate effect. Dabigatran is presently used after hip and knee replacement surgery to prevent thromboembolism.

Another group of relatively new anticoagulants are the Factor Xa inhibitors. **Fondaparinux** is a Factor Xa inhibitor. Fondaparinux is used subcutaneously, and is effective quite quickly. Fondaparinux is used to prevent thromboembolism after hip-fracture, and hip or knee replacement.

13.2.5 Fibrinolysis and fibrinolytics

Fibrinolysis or thrombolysis is the breakdown of clots. The breakdown of clots is a normal process, and is uses **plasmin** as the active fibrinolytic agent. Plasmin breaks down both the soluble fibrin and the insoluble fibrin (Figure 23.3). When there is excessive clotting and thrombus formation, drugs are used to activate fibrinolysis. **Streptokinase** activates the

plasma form of plasminogen to produce plasmin, whereas **alteplase** activates the fibrin form of plasminogen, also to form plasmin for fibrinolysis (Figure 13.6).

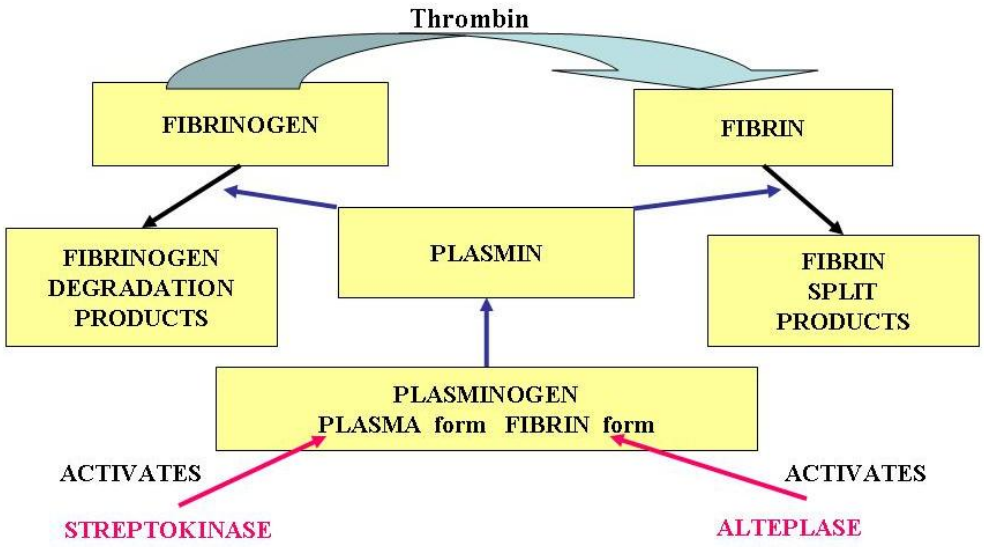

Figure 13.6 Mechanism of fibrinolytics (Copyright QUT, Sheila Doggrell)

As **streptokinase** activates the plasma form of plasminogen, it has widespread effects. It will breakdown thrombi, but it will also breakdown clots, where blood vessel repair is taking place. These widespread effects of streptokinase lead to a high incidence of bleeding. Streptokinase is derived from hemolytic streptococci, a streptococci that breaks down blood clots. Streptokinase is quite antigenic, which can lead to allergic reaction, and even severe allergic reaction such as anaphylaxis. Streptokinase is administered intravenously, and to get a good break down of clots, a loading dose is used and this is followed with a maintenance dose.

Alteplase is the generic or non-proprietary name for tissue type plasminogen activator (also known as TPA). It is claimed that alteplase selectively activates fibrin form of plasminogen, which means it will be clot selective. It was initially claimed that would lead to less bleeding than with streptokinase, but bleeding is a common adverse effect with streptokinase and alteplase. Alteplase is prepared by recombinant DNA. Alteplase is administered intravenously, and a loading and then maintenance dose is used to get the maximum effect.

Both streptokinase and alteplase are used to cause the **breakdown of clots**, and this included the clots causing **multiple pulmonary emboli**, **deep vein thrombosis**, **acute myocardial infarction**, and **stroke**.

13.3 Lipid modulating drugs

High levels of cholesterol (**hypercholesterolemia**) or **dyslipidemia** (altered levels of cholesterol, some up, some down) lead to **atherosclerosis**. Dyslipidemia is commonly associated with **diabetes**. Atherosclerosis can cause myocardial infarction, peripheral vascular disease, and stroke, often ultimately leading to death. Atherosclerosis can also contribute to angina, heart failure or cerebrovascular disease, which can also be deadly, often after progressing to heart attacks and strokes. Atherosclerosis is not the only risk factor for most of these conditions. For instance, other risk factors for coronary heart disease are age,

family history of premature coronary heart disease including diabetes, cigarette smoking, and obesity.

13.3.1 Cholesterol

Cholesterol is good for you! That is, provided it is **at normal levels**, where it is used in membrane synthesis, steroid hormone synthesis and the synthesis of bile acid. It is only excessive cholesterol that leads to **atherosclerosis**. Dietary fat is broken down successively to chylomicrons, chylomicron remnants, very low density lipoproteins (VLDL), intermediate density lipoproteins (IDL), **low density lipoproteins** (LDL), triglycerides and **high density lipoprotein** (HDL). VLDL and IDL are carriers of triglycerides and LDL and HDL are carriers of cholesterol (also known as LDL-cholesterol etc). LDL-cholesterol is the major reservoir of cholesterol in human plasma (60-70% of total cholesterol).

If you decrease the level of LDL cholesterol "**the bad cholesterol**", there is a decreased risk of atherosclerosis, and its consequences. Conversely, if you increase the HDL cholesterol "**the good cholesterol**", there is a substantial decreased risk of atherosclerosis.

High LDL cholesterol is considered to be 4.94 mmol/L or above, and **low HDL cholesterol** is 0.75 mmol/L or lower. Drug treatment is available to decrease LDL cholesterol and increase HLD cholesterol.

13.3.2 Statins

The levels of **LDL cholesterol** are commonly **decreased** by using the statins, which are HMG CoA reductase (hydroxyl-methylglutaryl coenzyme A-reductase) inhibitors. When the liver needs cholesterol to synthesise membranes, steroids or bile salts, it increases the number of **LDL receptors**. These LDL receptors are required to capture the plasma LDL cholesterol for the synthesis (Figure 24.1). One of the enzymes involved in this pathway is **HMG CoA reductase**. When this enzyme is inhibited, there is an increased synthesis of LDL receptors and LDL cholesterol removal from the plasma.

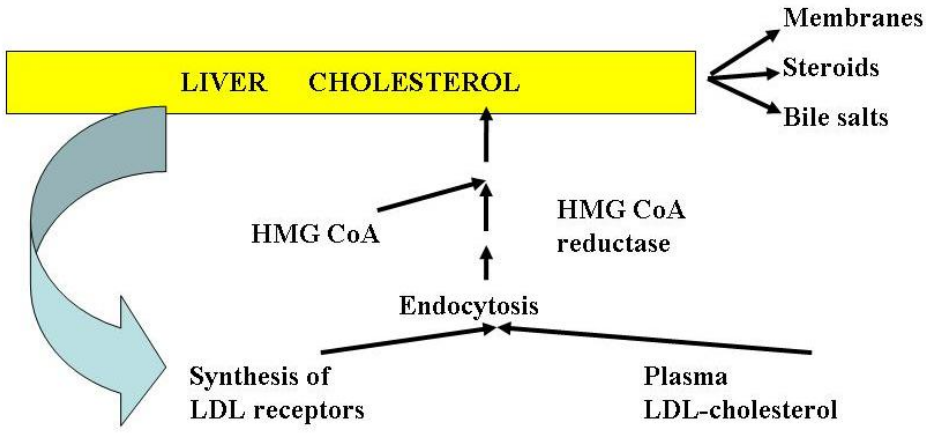

Figure 13.7 HMG CoA reductase (Copyright QUT, Sheila Doggrell)

Simvastatin and all the other statins were developed as inhibitors of HMG CoA reductase. Inhibition of HMG CoA reductase with a statin leads to decreased cholesterol synthesis, and increased synthesis of LDL receptors to decrease plasma LDL-cholesterol. The statins have been shown to decrease mortality and morbidity in subjects with coronary heart disease or at **high cardiovascular risk** e.g. diabetes. They are preferred to all other agents that have been

used to decreased LDL cholesterol, as statins have a lower incidence of side effects than other agents.

13.3.3 Fibric acid derivatives

The fibric acid derivates (fibrates) e.g. **gemfibrozil**, are used to **increase HDL cholesterol** especially in subjects who have low HDL cholesterol levels e.g. diabetics. The fibrates bind to Peroxisome Proliferation-Activated Receptor (**PPAR)α**, a nuclear receptor that regulates gene expression, and stimulate it. PPARα stimulates fatty acid oxidation to reduce the levels of triglycerides, and stimulates lipoprotein lipase to clear triglycerides, and increases HDL-cholesterol. As a result of these actions, the fibric acid derivatives **decrease levels of triglycerides**, have variable small effects on LDL-cholesterol, but **increase the levels of HDL-cholesterol**. The fibrates are used in subjects with high levels of triglycerides and low levels of HDL-cholesterol, which commonly occurs in the **metabolic syndrome** (obese, hypertensive, dyslipidemia) and **diabetes**.

13.3.4 Ezetimibe

Ezetimibe inhibits the transporter for cholesterol absorption from the gastrointestinal tract, and this reduces cholesterol absorption. This leads to decreased levels of plasma LDL cholesterol, but has little effect on HDL cholesterol and triglycerides. Ezetimibe is active after oral administration. It undergoes extensive enterohepatic recycling. Ezetimibe can be used alone in subjects with high LDL cholesterol levels, but the statins are usually preferred for monotherapy. A few people cannot tolerate statins, as it can cause myopathy (muscle weakness), and then ezetimibe is used as an alternative to statins to lower LDL cholesterol. More commonly, ezetimibe is used in combination with simvastatin, when the simvastatin alone fails to lower LDL cholesterol sufficiently. Ezetimibe and simvastatin have different mechanisms of action, and this allows them to have an additive effect when combined to lower LDL cholesterol.